

Treating pelvic inflammatory disease with doxycycline and metronidazole or penicillin and metronidazole.

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SUMMARY The best way of treating pelvic inflammatory disease (PID) is not known. The clinical response to two treatment regimens (penicillin plus metronidazole v doxycycline plus metronidazole) was studied in 33 patients with PID confirmed by laparoscopy and endometrial biopsy. The overall failure rate, according to the criteria used in this study was five of 11 (45%) women with chlamydial PID, none of six women with gonococcal PID, all of four women with chlamydial gonococcal PID, and three (25%) of 12 women with non-chlamydial non-gonococcal PID. The failure rate with penicillin plus metronidazole treatment was unacceptably high (53%), and significantly higher than that with doxycycline plus metronidazole (19%) ($p=0.038$). In most cases the microbiological and histopathological evaluations identified a probable explanation for the poor response to the treatment regimen used.

Introduction

Acute pelvic inflammatory disease (PID) is usually an ascending polymicrobial infection of the endometrium and fallopian tubes.¹⁻³ Though laparoscopy and endometrial sampling have improved its diagnosis,^{4,5} the microbial aetiology of tubal infection is rarely known. Thus antimicrobial treatment should cover all common causative organisms.^{6,7} Previous studies have shown that roughly 15%-20% of patients with acute PID fail to respond to initial treatment, and in up to 30% the disease recurs.²

This study aimed to evaluate the efficacy of two antimicrobial combinations commonly used in the treatment of acute PID.

Patients and methods

The study group comprised 33 women who had

laparoscopically diagnosed salpingitis or histopathologically diagnosed endometritis, or both. The presence of salpingitis was assessed using the laparoscopic criteria of mild, moderate, or severe salpingitis,⁸ and a single strip endometrial biopsy specimen was obtained, as described.⁵ The histopathological diagnosis of endometritis was based on the presence of plasma cells on endometrial biopsy. Endometritis was classified as mild, moderate, or severe.⁵ Cervical, endometrial, tubal and peritoneal cultures for isolation of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, herpes simplex virus, and anaerobic and facultative bacteria were obtained as described previously.⁴ We classified all cases according to the culture results for *C trachomatis* and *N gonorrhoeae* as follows: chlamydial PID, if *C trachomatis* but not *N gonorrhoeae* was isolated from any site; gonococcal PID, if *N gonorrhoeae* but not *C trachomatis* was isolated from any site; chlamydial gonococcal PID, if both organisms were isolated; and non-chlamydial non-gonococcal PID, if neither organism was isolated.

Antimicrobial treatment was started intravenously

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immediately after laparoscopy. The patients were unselectively treated either with the combination of penicillin plus metronidazole or doxycycline plus metronidazole. The patients with an even year of birth were given intravenous benzylpenicillin 1.8 g three times a day plus metronidazole 500 mg three times a day for 48 hours, followed by 660 mg phenoxymethyl penicillin plus 400 mg metronidazole three times a day by mouth to complete 14 days of treatment. The women with an odd year of birth were given intravenous doxycycline hydrochloride 100 mg twice daily plus metronidazole 500 mg three times a day intravenously for 48 hours, followed by 150 mg doxycycline once daily plus metronidazole 400 mg three times per day by mouth to complete 14 days of treatment.

A clinical severity score was derived by grading the presence of cervical motion and uterine and adnexal tenderness on a scale of 0 (absent to normal) to 3 (severe), as described previously.⁹ An intrauterine contraceptive device (IUCD) was present in 14 patients, which was removed before the start of treatment. The clinical examination was repeated 48–72 hours, seven days, and 14 to 16 days after treatment had been started. Cervical cultures for *C trachomatis* and *N gonorrhoeae* were repeated at the 14 to 16 days visit. Erythrocyte sedimentation rate, serum C reactive protein concentration,¹⁰ and white cell count were determined initially. The erythrocyte sedimentation rate and white cell count were repeated after 14 days of treatment.

Treatment failure was defined as follows: no improvement in the clinical severity score during pelvic examination performed 48–72 hours after the start of treatment; presence of pelvic mass, clinical severity score ≥ 5 , positive cervical culture for *N gonorrhoeae* or *C trachomatis*, or erythrocyte sedimentation rate higher than half of the initial level at the 14 to 16 days examination.

Fisher's exact test was used for statistical comparisons.

Results

Table I shows that the demographic and clinical characteristics of the patient groups were comparable. Seventeen patients were treated with penicillin plus metronidazole, and 16 were treated with doxycycline plus metronidazole.

Table II summarises the response to treatment in 17 patients who received penicillin plus metronidazole. According to our criteria the treatment had failed in nine (53%) cases, including three (75%) of four patients with chlamydial PID, four (100%) women with chlamydial gonococcal PID, and two (50%) of four women with non-chlamydial non-gonococcal PID.

TABLE I Selected characteristics and clinical findings in women treated for acute pelvic inflammatory disease (PID)

Observation	Penicillin and metronidazole	Doxycycline and metronidazole
No of patients	17	16
Age (years)*	26 (9)	23 (4)
Nulliparous	8	8
Contraception		
IUCD	9	5
Hormonal	2	4
Other methods	4	4
None	2	3
History of PID	3	7
Duration of symptoms (days)*	11 (7)	8 (8)
Clinical severity score*	11 (5)	11 (5)
Erythrocyte sedimentation rate (mm/hour)*	34 (23)	35 (24)
C reactive protein (mg/l)*	67 (54)	53 (44)

* Values are mean (SD).

TABLE II Occurrence of treatment failures in relation to isolation of *Chlamydia trachomatis* or *Neisseria gonorrhoeae* in 33 patients treated for acute pelvic inflammatory disease (PID)

Classification of PID	No of failures/No treated with:	
	Penicillin and metronidazole	Doxycycline and metronidazole
Chlamydial	3/4	2/7
Gonococcal	0/5	0/1
Chlamydial gonococcal	4/4	0/0
Non-chlamydial non-gonococcal	2/4	1/8
Total (%)	9/17 (53)	3/16 (19)

Table III shows the microbiological findings and severity of endometritis and salpingitis in patients treated with penicillin plus metronidazole. Of eight women who had PID associated with *C trachomatis* infection, seven (88%) failed to respond to penicillin plus metronidazole treatment (tables II and III). In both patients with non-chlamydial non-gonococcal PID in whom treatment failed *Escherichia coli*, or *Haemophilus influenzae*, was isolated from the fallopian tubes (table III). In one case *H influenzae* was isolated from tubal aspirate, and in the other *E coli* was isolated from the tube and the endometrium. In one patient (case 7) who responded clinically *E coli* was isolated from the fallopian tube. Anaerobic bacteria were isolated from the endometrium in seven cases. Patients who had not responded to penicillin plus

TABLE III Isolation of micro-organisms, severity of endometritis and salpingitis, and treatment response in 17 women treated with penicillin plus metronidazole and in 16 (cases 18-33) treated with doxycycline plus metronidazole.

Case No	Culture results		Classification of PID*	Severity of endometritis†	Severity of salpingitis‡	Treatment failure
	Cervix	Endometrium				
1	Ct, Gc, Mh	Ct, Gc, Mh, <i>Streptococcus agalactiae</i>	CG	Severe	Severe	Yes
2	Mh	Ct, anaerobic streptococcus	C	Severe	Mild	No
3	Uu	<i>Bacillus cereus</i>	NCNG	Normal finding	Mild	No
4	Gc		G	Severe	Mild	No
5	Ct, Gc, Mh	Gc	CG	Moderate	Mild	Yes
6	Gc, Uu, HSV		G	Moderate	Severe	No
7	Gc		NCNG	Mild	Mild	No
8	Ct, Gc, Uu	<i>E coli</i>	G	Severe	Severe	No
9	Ct, Gc, Uu	Gc	CG	Moderate	Normal finding	Yes
10	Ct	Ct, <i>Peptostreptococcus</i>	C	Severe	Severe	Yes
11	Gc, Mh, Uu, HSV	Ct, <i>Peptostreptococcus</i>	G	Moderate	Normal finding	No
12	Mh	Gc, Mh, <i>Bacteroides bivius</i> HSV	NCNG	Moderate	Severe	Yes
13	Gc, Uu	<i>Peptostreptococcus</i>	G	Mild	Moderate	No
14	Ct	Ct	C	Severe	Normal finding	Yes
15	Ct, Uu	<i>Escherichia coli</i>	NCNG	Mild	Moderate	Yes
16	Ct, Uu	Ct	C	Mild	Mild	Yes
17	Ct, Gc		CG	Moderate	Mild	Yes
18	Mh, HSV		NCNG	Moderate	Mild	No
19	Ct, Mh		C	Mild	Mild	No
20	Mh	Mh, microaerophilic streptococci	NCNG	Mild	Moderate	No
21	Ct, Mh, Uu	Mh, Uu, <i>Staphylococcus aureus</i>	C	Moderate	Moderate	No
22	Ct, Uu	Ct, HSV	C	Severe	Moderate	Yes
23	Uu	Sir α -haemolyticus	NCNG	Normal finding	Moderate	No
24	HSV	<i>Bacteroides bivius</i> , HSV	NCNG	Mild	Mild	No
25	Ct	Ct	C	Severe	Mild	No
26		<i>B bivius</i>	NCNG	Mild	Mild	No
27		Sir α -haemolyticus	NCNG	Normal finding	Mild	No
28	Ct, Uu	Ct	C	Severe	Moderate	No
29		<i>H influenzae</i>	C	Severe	Severe	No
30		<i>B melaninogenicus</i>	NCNG	Severe	Severe	Yes
31	Gc		G	Mild	Mild	No
32	Ct	Ct	C	Severe	Mild	Yes
33			NCNG	Normal finding	Mild	No

† Detected by endometrial biopsy. ‡ Detected by laparoscopy.

Ct = *Chlamydia trachomatis*, Gc = *Neisseria gonorrhoeae*, Mh = *Mycoplasma hominis*, Us = *Ureaplasma urealyticum*, HSV = herpes simplex virus. C = Chlamydial, G = gonococcal, CG = chlamydial gonococcal, NCNG = non-chlamydial non-gonococcal.

metronidazole were subsequently treated with doxycycline (three cases), or with the combination of sulphadiazine plus trimethoprim (four cases), or with amoxycillin (two cases).

Table III summarises the findings and clinical response in the 16 patients who were treated with doxycycline plus metronidazole. This treatment regimen failed in three (19%) patients, including two of seven (29%) with chlamydial PID and one of eight (12%) patients with non-chlamydial non-gonococcal PID (tables II and III). *Bacteroides melaninogenicus* was isolated from the fallopian tubes in the patient with non-chlamydial non-gonococcal PID who failed to respond. She developed pelvic peritonitis with a tubal abscess, which was aspirated three times. *Actinomyces israelii* was isolated from the removed IUCD.

The severity of endometritis seemed to predict treatment failure slightly better than the severity of salpingitis. Thus treatment failure occurred in six of 12 women (50%) with severe endometritis, and three of seven women (43%) with severe salpingitis (table III).

Discussion

Optimal treatment for PID is difficult to determine for the following reasons: the microbial aetiology of tubal infection is rarely known; a uniform objective clinical scoring system to evaluate the short term response to treatment has not been widely used; and long term follow up studies for tubal infertility after antimicrobial treatment are extremely difficult. In this study we used the clinical scoring system for tenderness developed by McCormack *et al*⁹ to assess the clinical response to antimicrobial treatment. We also used laparoscopy, endometrial biopsy, and microbiological sampling of the cervix, endometrium, tubes, and peritoneal cavity to obtain objective evidence of the presence, severity, and aetiology of PID.

Both single drug and combination drug treatments have been used in the treatment of acute PID. Failure rates of previous treatment trials have ranged from 0%–55% (mean 12%).^{11–12} The failure rate for the combination of penicillin plus metronidazole in this study was unacceptably high (53%). This is undoubtedly due to the fact that penicillin or metronidazole are not effective against *C trachomatis*. Our findings agree with those of previous studies on women with cervicitis.¹³

Doxycycline plus metronidazole has been recommended for the treatment of acute PID by the Centers for Disease Control, United States of America.¹⁴ This combination is effective against both anaerobes and *C trachomatis*. In this trial the failure rate was 19%, which is significantly ($p=0.038$) lower than that for

penicillin plus metronidazole (53%). Our results agree with those of previous studies.^{15–20} In two of three cases with no response to doxycycline plus metronidazole *C trachomatis* was isolated from the cervix, endometrium, and fallopian tubes. Severe plasma cell endometritis was detected by endometrial biopsy. The dose, or the duration of the treatment, may have been insufficient. Resistance to doxycycline among *C trachomatis* strains has not been described.

Histopathological examination showed severe endometritis in 12 patients, and in eight of these *C trachomatis* was also isolated from the endometrium. Remarkably, severe endometritis was detected in 50% of the patients who failed to respond to the antimicrobial treatment. This finding deserves further study. Perhaps the presence of severe endometritis predicts the failure of conventional treatment. In such cases, therefore, the treatment should be more effective with higher doses and longer duration. Serial determinations of serum C reactive protein might also be helpful in monitoring response to the treatment.

As previous studies have shown a high rate of anaerobic bacteria in the peritoneal fluid, or endometrial cavity, of women with PID, we combined metronidazole with both the antimicrobial agents used to gain better coverage against anaerobic bacteria. In such studies, however, the specimens were obtained by culdocentesis, or transcervically, so that vaginal contamination of the specimens might have occurred.^{3,15,21} In this study we found a much lower prevalence of anaerobic bacteria in the endometrial and tubal specimens. The use of metronidazole is probably unnecessary in the treatment of uncomplicated PID without pelvic abscesses. On the other hand, in this study mixed facultative and anaerobic bacteria were commonly found in the endometrial specimens, supporting the argument for using metronidazole in the combination treatment, though the possibility of cervicovaginal contamination is extremely difficult to rule out when any transcervical sampling method is used.

E coli, *H influenzae*, and *B melaninogenicus* were examples of non-gonococcal and non-chlamydial organisms isolated directly from the fallopian tubes. Three such cases did not respond to the initial treatment. These findings stress the importance of obtaining microbiological specimens directly from the inflamed tubes. Laparoscopy is necessary to obtain these specimens and to evaluate the severity of the disease. In two cases *H influenzae* was isolated from tubo-ovarian abscesses when these abscesses were aspirated under laparoscopic control. In addition to appropriate antimicrobial treatment and laparoscopic damage of abscess, further surgical interventions were not required in any of the cases.

In conclusion, our study clearly shows that penicillin plus metronidazole is an inadequate treatment for acute PID. Doxycycline plus metronidazole treatment showed a significantly lower (19%) clinical failure rate. We were able to identify a reasonable microbiological or histopathological explanation for the poor response in most cases of treatment failure. This emphasises the importance of extensively evaluating patients with suspected PID.

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